REMARKS

I. Amendments

The specification has been amended to correct minor typographical and grammatical errors. For the sake of brevity, characterization data (mp, NMR shift values) was not included at the end of paragraphs related to experimental data. It is intended that the experimental data remain in the application. These changes introduce no new matter into the specification.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached pages are captioned "Version with Markings to Show Changes Made".

No change in inventorship is necessitated by the amendments.

II. Conclusion

Consideration of the claims is solicited. Should the Examiner believe that a conference with Applicants' Attorney would advance prosecution of this application, the Examiner is respectfully requested to call Applicants' Attorney.

Respectfully submitted,

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Version with Markings to Show Changes Made

In the Specification

Page 2, paragraph 2 (AMENDED)

In order to investigate an anti-AIDS drug having CCR5 antagonistic activity, it is necessary to clone CCR5 gene from human tissue derived cDNA library, to ligate said gene with a vector for expression in animal cells, to introduce said gene into animal cells and to obtain cells expressing CCR5. In addition, with using this transformant, it is necessary to screen a compound which strongly inhibits binding of CC chemokine RANTES, natural ligand, to CCR5. However, so far there has been almost no report **[on]** **of** a low **[molecule]** **molecular weight** compound which has this CCR5 antagonistic activity and is suitable for oral administration. The present invention is to provide a novel anilide derivative which is useful for the treatment or prevention of infectious diseases of HIV and, in particular, AIDS and also which is suitable for oral administration, production and use thereof.

Page 6, paragraph 1 (AMENDED)

(18) The compound as described in the above (17), wherein the alicyclic hydrocarbon group is a lower cycloalkyl group;

(19) The compound as described in the above (17), wherein the alicyclic hydrocarbon group is cyclohexyl;

(20) The compound as described in the above (17), wherein the alicyclic heterocyclic group is a saturated alicyclic heterocyclic group;

(21) The compound as described in the above (17), wherein the alicyclic heterocyclic

group is tetrahydropyranyl, tetrahydrothiopyranyl or piperidyl;

(22) The compound as described in the above (17), wherein the alicyclic heterocyclic group is tetrahydropyranyl;

(23) The compound selected from the class consisting of 7-(4- **[ethoxyethoxephenyl]** **ethoxyethoxyphenyl**)-1-ethyl-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1-benzazepine-4- **[carbiboxamide]** **carboxamide**; 1-ethyl-7-(4-propoxyethoxyphenyl)-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide; 7-(4-butoxyethoxyphenyl)-1-ethyl-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide; 7-(4-ethoxyethoxyphenyl)-1-formyl-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1-

Page 12, paragraph 1 (AMENDED)

treatment or **[prebention]** **prevention** of infectious diseases of HIV;

(36) A method for antagonizing a CC chemokine receptor (CCR) in a mammal, which comprises administering an effective amount of a compound described in the above (1) or a salt thereof to a mammal;

(37) Use of a compound described in the above (1) or a salt thereof in preparation of a medicament for antagonizing a CC chemokine receptor (CCR); etc.

Page 14, paragraph 1 (AMENDED)

as cyclopropylmethyl, cyclobutylmethyl, **[cyclopentylmehyl,]** **cyclopentylmethyl,** cyclohexylmethyl, cycloheptylmethyl, etc.), and the like.

Page 16, paragraph 1 (AMENDED)

pyrazolidine, pyrazoline, piperidine, piperazine, oxazine, oxadiazine, thiazine, **[thaziadine,]** **thiadiazine,** morpholine, thiomorpholine, pyran and tetrahydropyran, as well as non-aromatic **[heterocycle]** **heterocycles** in which **[a par]** **some** or **[whole bond(s)]** **all of the bonds** of the aforementioned **[aromatic]** **non-aromatic** heterocycle **[is (are) a]** **are** saturated **[bond]** **bonds**, and the like (preferably, aromatic **[heterocycle]** **heterocycles** such as pyrazole, thiazole, oxazole, tetrazole, etc.).

Page 19, paragraph 1 (AMENDED)

of the C_{3-7} cycloalkyl include cyclopropyl**[.],** cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, etc. Among others, a straight C_{1-6} lower alkyl is preferable and C_{1-3} lower alkyl is more preferable. The groups R^7 and R^8 may be the same or different, and preferably the groups R^7 and R^8 are the same. When R^7 and R^8 may bind to each other to form a 5- to 7- membered ring, the groups R^7 and R^8 bind to each other to represent a straight C_{2-4} alkylene chain of the formula: $-(CH_2)_2-$, $-(CH_2)_3-$, $-(CH_2)_4-$, etc. Said chain may have a substituent, and examples of the substituent include hydroxy group, halogen, etc.

Page 19, paragraph 2 (AMENDED)

Examples of the optionally esterified carboxyl group include a carboxyl group and an ester formed by binding a carboxyl group to a C_{1-6} alkyl group or a C_{3-7} cycloalkyl group (e.g., methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, **[isoprpoxycarbonyl,]** **isopropoxycarbonyl,** butoxycarbonyl, isobutoxycarbonyl, sec-butoxycarbonyl, tert-butoxy-carbonyl, pentyloxycarbonyl, hexyloxycarbonyl, etc.).

Page 22, paragraph 1 (AMENDED)

methoxymethoxy, methoxyethoxy, ethoxyethoxy, trifluoromethoxyethoxy, trifluoroethoxyethoxy, etc.), formyl, C_{2-4} alkanoyl (e.g. acetyl, propionyl, etc.), **[C1-4]** **C_{1-4}** **[alkylsuflonyl]** **alkylsulfonyl** (e.g. methanesulfonyl, ethanesulfonyl, etc.), etc., and the number of **[the]** substituents **[are preferable]** **is preferably** 1 to 3.

Page 31, paragraph 1 (AMENDED)

sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, octyl, nonyl, decyl, etc., preferably lower (C_{1-6}) alkyl, etc.);

(3) an optionally substituted cycloalkyl (e.g. C_{3-7} cycloalkyl, etc. such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, etc.);

(4) an optionally substituted alkenyl (e.g., C_{2-10} alkenyl such as allyl, crotyl, 2-pentenyl, 3-hexenyl, etc., preferably lower (C_{2-6}) alkenyl, etc.);

(5) an optionally substituted cycloalkenyl (e.g. C_{3-7} cycloalkenyl, etc. such as 2-cyclopentenyl, 2-cyclohexenyl, 2-cyclopentenylmethyl, 2-cyclohexenylmethyl, etc.);

(6) an optionally substituted 5-to 6-membered monocyclic aromatic group (e.g., phenyl, 5-to 6-membered aromatic heterocyclic group (e.g., 5- to 6-membered aromatic heterocyclic group containing 1 to 4 hetero-atoms consisting of 1 to 2 kinds of hetero-atoms selected from oxygen atom, sulfur atom and nitrogen atom, such as furyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, oxazolyl, isothiazolyl, isoxazolyl, tetrazolyl, pyridyl, pyrazyl, **[pirimidinyl]** **pyrimidinyl**, pyridazinyl, triazolyl, etc.);

(7) an optionally substituted 5- to 6-membered monocyclic non-aromatic heterocylic group (e.g., a group which is formed by removing one hydrogen atom from a 5- to 6-

Page 33, paragraph 1 (AMENDED)

substituted thiol group (e.g., thiol, C_{1-4} alkylthio, etc.), an optionally substituted amino group (e.g., amino; **[meno]** **mono** -C_{1-4} alkylamino; di-C_{1-4} alkylamino; 5- to 6- membered cyclic amino such as tetrahydropyrrole, piperazine, piperidine, morpholine, thiomorpholine, pyrrole, imidazole, etc.; etc.), an optionally esterified or amidated carboxyl group (e.g. carboxyl, C_{1-4} alkoxy-carbonyl, carbamoyl, mono-C_{1-4} alkylcarbamoyl, di-C_{1-4} alkylcarbamoyl, etc.), an optionally halogenated C_{1-4} alkyl (e.g., trifluoromethyl, methyl, ethyl, etc.), an optionally halogenated C_{1-4} alkoxy (e.g. methoxy, ethoxy, propoxy, butoxy, trifluoromethoxy, trifluoroethoxy, etc.), C_{1-4} alkylenedioxy (e.g., $-O-CH_2-O-$, $-O-CH_2-CH_2-O-$, etc.), optionally substituted sulfonamide [e.g., an optionally substituted amino group (e.g. amino; mono-C_{1-4} alkylamino; di-C_{1-4} alkylamino; 5- to 6-membered cyclic amino such as tetrahydropyrrole, piperazine, piperidine, morpholine, thiomorpholine, pyrrole, imidazole, etc.) which is bound to $-SO_2-$, etc.], formyl, C_{2-4} alkanoyl (e.g., acetyl, propionyl, etc.), C_{1-4} alkylsulfonyl (e.g., methanesulfonyl, ethanesulfonyl, etc.), etc., and the number of the substituents are preferably 1 to 3.

Page 35, paragraph 1 (AMENDED)

include halogen (e.g., fluorine, chlorine, bromine, iodine, etc.), nitro, cyano, hydroxy group, an optionally substituted thiol group (e.g., thiol, C_{1-4} alkylthio, etc.), an optionally substituted amino group (e.g., amino; mono-C_{1-4} alkylamino; di-C_{1-4} alkylamino; 5- to 6- membered cyclic amino such as tetrahydropyrrole, piperazine, piperidine, morpholine, thiomorpholine, pyrrole, imidazole, etc.; etc.), an optionally esterified or amidated carboxyl group (e.g., carboxyl, C_{1-4} alkoxycarbonyl, carbamoyl, mono-C_{1-4} alkyl carbamoyl, di-C_{1-4} alkylcarbamoyl, etc.), an optionally halogenated C_{1-4} alkyl, (e.g., trifluoromethyl, methyl, ethyl, etc.), an optionally halogenated C_{1-4} alkoxy (e.g., methoxy, ethoxy, propoxy, butoxy, trifluoromethoxy,

trifluoroethoxy, etc.), formyl, C_{2-4} alkanoyl (e.g., acetyl, propionyl, etc.) C_{1-4} alkylsulfonyl (e.g., methanesulfonyl, ethanesulfonyl, etc.), etc., and the number of **[the substitutes are]** **substituents is** preferably 1 to 3.

Page 35, paragraph 2 (AMENDED)

Examples of the optionally amidated carboxyl group as the **[substitutes]** **substituent** for R^1 include **[an]** **a** carbonyl group binding to "an optionally substituted amino group", etc. which is the same as that of the above-described "optionally substituted amino group as the substituents for R^1" and among others, carbamoyl, mono-C_{1-6} alkylcarbamoyl, di-C_{1-6} alkylcarbamoyl, etc. are

Page 38, paragraph 1 (AMENDED)

aromatic ring which has a group of the formula: $R\text{-}Z^1\text{-}X\text{-}Z^2$- wherein each symbol is as defined above, and which may have a further substituent" represented by R^1 may have, in addition to the group of the formula: $R\text{-}Z^1\text{-}X\text{-}Z^2$-, include, in particular, a lower (C_{1-4}) alkyl optionally substituted with a halogen or a lower (C_{1-4}) alkoxy (e.g., methyl, ethyl, t-butyl, trifluoromethyl, methoxymethyl, ethoxymethyl, propoxymethyl, butoxymethyl, methoxyethyl, ethoxyethoxy, propoxyethyl, butoxyethyl, etc.), a lower (C_{1-4}) alkoxy optionally substituted with a halogen or a lower (C_{1-4}) alkoxy (e.g., methoxy, ethoxy, propoxy, butoxy, t-butoxy, trifluoromethoxy, methoxymethoxy, ethoxymethoxy, propoxymethoxy, butoxymethoxy, methoxyethoxy, ethoxyethoxy, propoxyethoxy, butoxyethoxy, methoxypropoxy, ethoxypropoxy, propoxypropoxy, butoxypropoxy, etc.), halogen (e.g., fluorine, chlorine, etc.), nitro, cyano, an amino group optionally substituted with 1-2 lower (C_{1-4}) alkyl groups, formyl group or lower (C_{2-4}) alkanoyl groups (e.g., amino, methylamino, dimethylamino, **[fromylamino]** **formylamino**, **[acethylamino]** **acetylamino**, etc.), 5- to 6-membered cyclic amino (e.g., 1-pyrrolidinyl, 1-

piperazinyl, 1-piperidinyl, 4-morpholino, 4-thiomorpholino, 1-imidazolyl, 4-tetrahydropyranyl, etc.), etc.

Page 41, paragraph 2 (AMENDED)

In the above formula (I), examples of the "optionally substituted aliphatic hydrocarbon group" (aliphatic straight chain hydrocarbon group and aliphatic cyclic hydrocarbon group) represented by R^2 and R^3 include (1) an optionally substituted alkyl (e.g., C_{1-10} alkyl such as methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl, hexyl, heptyl, octyl, nonyl, decyl, etc., preferably lower (C_{1-6}) alkyl, etc.);
(2) an optionally substituted cycloalkyl (e.g. C_{3-8} cycloalkyl such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, etc.; etc.), provided that
(2-1) said cycloalkyl may contain one hetero-atom selected from a sulfur atom, an oxygen atom and a nitrgen atom to form oxirane, **[thiorane]** **thiolane**, aziridine, tetrahydrofuran, tetrahydrothiophene, pyrrolidine, tetrahydropyran, tetrahydrothiopyran, tetrahydrothiopyran-1-oxide, piperidine, etc. (preferably, 6-membered ring

Page 47, paragraph 2 (AMENDED)

As the compound represented by the above formula (I), 7-(4-ethoxyethoxyphenyl)-1-ethyl-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide; 1-ethyl-7-(4-propoxyethoxyphenyl)-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide; 7-(4-butoxyethoxyphenyl)-1-ethyl-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide; 7-(4- **[ethoxythoxyphenyl]** **ethoxyethoxyphenyl**)-1-formyl-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide; 1-formyl-7-(4-propoxyethoxyphenyl)-N-[4-[[N-methyl-N-

(tetrahydropyran-4- **[rl]** yl)amino]methyl]phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide; 7-(4-butoxyethoxyphenyl)-1-formyl-N-[4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1-benzazepine-4-carboxamide; 7-(4-butoxyethoxyphenyl)-N-[4-[[N-methyl-N-(tetrahydropyran-5-yl)amino]methyl]phenyl]-1-propyl-2,3-dihydro-1-benzazepine-4-carboxamide; N-[4-[[N-methyl-N-(tetrahydropyran-5-

Page 54, paragraph 1 (AMENDED)

antioxidant, a colorant, a sweetener, etc. may be used. Suitable examples of the excipient include lactose, sucrose, D-mannitol, starch, crystalline cellulose, light silicic acid anhyride, etc. Suitable examples of the lubricant include magnesium stearate, calcium stearate, talc, colloidal silica, etc. Suitable examples of the binder include crystalline cellulose, sucrose, D-mannitol, dextrin, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, polyvinyl-pyrrolidone, etc. Suitable examples of the disintegrating agent include starch, carboxymethyl cellulose, carboxymethyl cellulose calcium, croscarmellose sodium, sodium carboxymethyl starch, etc. Suitable examples of the solvent include water for injection, alcohol, propylene glycol, macrogol, sesame oil, corn oil, etc. Suitable examples of the solubilizer include polyethylene glycol, propylene glycol, D-mannitol, benzyl benzoate, ethanol, trisaminomethane, cholesterol, triethanolamine, sodium carbonate, sodium citrate, etc. Suitable examples of the suspending agent include surfactants such as stearyl triethanolamine, sodium laurylsulfate, laurylaminopropionic acid, lecithin, benzalkonium chloride, **[benzetonium]** **benzethonium** chloride, glycerin monostearate, etc.; hydrophilic polymers such as polvinylalcohol, polyvinylpyrrolidone, sodium carboxymethyl cellulose, methyl cellulose, hydroxymethyl

Page 55, paragraph 1 (AMENDED)

cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, etc. Suitable examples of the isotonizing agent include sodium chloride, glycerin, D-mannitol, etc. Suitable examples of the buffer include a buffer solution of phosphate, acetate, carbonate, citrate, etc. Suitable examples of the soothing agent include **[benzylacohol,]** **benzylalcohol,** etc. Suitable examples of the preservative include **[paraoxybenzoic]** **p-hydroxybenzoic** acid esters, chlorobutanol, benzylalcohol, phenethylalcohol, deydroacetic acid, sorbic acid, etc. Suitable examples of the antioxidant include sulfites, ascorbic acid, etc.

Page 61, paragraph 1 (AMENDED)

(1) Compound (I) can be produced by reacting Compound (I-1) or (I-2) with halogenated alkyl or halogenated aralkyl. Examples of a halogen atom include chlorine, bromine, iodine, etc. and usually about 1 to 2 moles of the halogenated alkyl or halogenated aralkyl is used per mole of Compound (I-1) or (I-2). If necessary, the reaction smoothly proceeds by addition of about **[once]** **equal** to **[thrice]** **three-fold** moles of a base such as triethylamine, diisopropylethylamine, pyridine, lithium hydride, sodium

Page 64, paragraph 2 (AMENDED)

Compound (I) having a tertiary amino group can be produced by reacting Compound (IV) and a secondary amine compound. Usually, about 1 to 3 moles of the secondary amine compound is used per mole of Compound (IV). If necessary, the reaction smoothly proceeds by addition of about **[once]** **equal** to **[thrice]** **three-fold** moles of a base such as triethylamine, diisopropylethylamine, pyridine, lithium hydride, sodium hydride, sodium methoxide, sodium ethoxide, sodium carbonate, potassium carbonate, sodium hydrogen carbonate and further sodium iodide, potassium iodide, etc. This substitution reaction is carried out in an inert solvent

such as methanol, ethanol, propanol, isopropanol, n-butanol, tetrahydrofuran, diethyl ether, dimethoxyethane, 1,4-dioxane, toluene, benzene, xylene, **[dichloromethane.]** **dichloromethane,** chloroform, 1,2-dichloroethane, dimethylformamide (DMF), dimethyl sulfoxide (DMSO), pyridine, etc., or a mixture of these solvents. The reaction temperature is generally about −10 °C to about 180 °C, and the reaction time is generally about 1 hour to about 40 hours. The reaction is carried out preferably under inert gas (e.g. nitrogen, argon, etc.) atmosphere.

[Method D]

Page 71, paragraph 2 (AMENDED)

The **[thus resulted]** **resultant** Compound (II) or (III) can be separated and purified with **[know]** **known** separation and purification methods such as concentration, concentration under reduced pressure, extraction, crystallization, solvent conversion, chromatography, etc.

Page 75, paragraph 2 (AMENDED)

When the compound of the formula (I) or a salt thereof is used in combination with a reverse transcriptase inhibitor and/or a protease inhibitor**[. The]** **, the** dose of the reverse transcriptase inhibitor or the protease inhibitor ranges, for example, from about 1/200-1/2 or more of **the** usual dose to about 2-3 times or less of **the** usual dose. In case that two or more drugs are used in combination, each dose of the drugs is appropriately adjusted if one drug affects metabolism of the other drug, while each dose of the drugs when they are used in combination is generally the same as the dose when they are used alone.

Page 79, paragraph 1 (AMENDED)

flask (Becton Dickinson) using Ham's F12 medium (Nihon Pharmaceutical) containing 10% fetal calf serum (Life Tech Oriental) and **[took]** **taken** off with 0.5 g/L trypsin-0.2g/L EDTA

(Life Tech Oriental). The cells were washed with PBS (Life Tech Oriental), centrifuged (1000 rpm, 5 minutes), and suspended in PBS. With using Gene Pulser (Bio-Rad Laboratories), DNA was introduced into the cells under the conditions shown below. That is, to the cuvette of 0.4 cm gap were added 8 x 10^6 cells and 10 μg of plasmid pCKR5 for expression of human CCR5, and electroporation was carried out under 0.25 kV of voltage and 960 μF of capacitance. The cells were transferred into Ham's F12 medium containing 10% fetal calf serum, and cultivated for 24 hours. The cells were again **[took]** **taken** off and centrifuged, and suspended in Ham's F12 medium containing 10% fetal calf serum and 500 μg/ml of geneticin (Life Tech Oriental). The suspension was diluted to give 104 cells/ml of the suspension, which was inoculated on **a** 96 well plate (Becton Dickinson) to give geneticin resistant cells.

Page 83, paragraph 1 (AMENDED)

potassium **[ferricyanade]** **ferricyanide**, 2 μM $MgCl_2$ and 0.4 mg/ml X-gal), and the mixture was allowed to stand at 37 °C for 50 minutes and washed twice with PBS. The number of blue cells was counted by a microscope and defined as the number of cells infected with HIV-1. According to this method, inhibition rate **[on]** **of** HIV-1 infection was determined. The results are shown in Table 2.

Page 90, paragraph 1 (AMENDED)

In DMF (12 ml) was suspended 7-(4- **[exthophenyl]** **ethoxyphenyl**)-1-methanesulfonyl-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (0.13 g). To the suspension was added, under ice-cooling, thionyl chloride (0.04 ml) and DMF (catalytic amount), and the mixture was stirred at room temperature for 2 hours. Under reduced pressure, the solvent was evaporated, and the residue was dissolved in THF (15 ml). The solution was added dropwise to a solution of 4-[N-methyl-N-(tetrahydro-2H-pyran-4-yl)aminomethyl]aniline (0.08 g) and triethylamine (0.14 ml)

in THF (5 ml), under ice-cooling, and the mixture was stirred under nitrogen atmosphere at room temperature overnight. Under reduced pressure, the solvent was evaporated. To the residue was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate, and the solvent was evaporated to give crude crystals, which were recrystallized from ethyl acetate/hexane to give 7-(4-ethoxyphenyl)-1-methanesulfonyl-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl]amino]methyl]phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxamide (0.16 g) as colorless crystals.

Page 98, paragraph 2 (AMENDED)

Reference Example 11

In water: ethanol: toluene (1:1: 10, v/v, 18.0 ml) were dissolved **[4-propokyphenyl]** **4-propoxyphenyl** borate (203 mg) and 7-bromo-1-methyl-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1H-benzazepine-4-carboxamide (455 mg). To the solution was added potassium carbonate (312 mg), and the mixture was stirred under argon atmosphere at room temperature for 30 minutes. To the mixture was added tetrakistriphenylphosphinepalladium

Page 103, paragraph 1 (AMENDED)

the mixture was stirred at room temperature for **[I]** **1** hour. Under reduced pressure, the solvent was evaporated, and to the residue was added THF (10.0 ml). On the other hand, to 4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]aniline dihydrochloride (158 mg) was added THF (10.0 ml), and then was added triethylamine (0.47 ml). To the obtained mixture was added dropwise at 0 °C the previously prepared acid chloride suspension, and the mixture was stirred at room temperature for 3 hours. To the mixture was added ethyl acetate, and the mixture was

washed with water, 1N sodium hydroxide solution, water and saturated brine. The organic layer was dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified with silica gel column chromatography (15 g, ethyl acetate → ethyl acetate: ethanol: triethylamine = 100: 10: 1), and recrystallized from ethanol to give 7-(4-ethoxy-3-fluorophenyl)-1-methylsulfonyl-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxamide (140 mg, 51 %) as white crystals.

Page 106, paragraph 1 (AMENDED)

bromobutyrate (82 ml). The mixture was stirred under nitrogen atmosphere at 85 °C for 24 hours, and to the mixture was added potassium t-butoxide (70 g) under ice-cooling. The mixture was stirred at 85 °C for 1.5 hours, and the solvent was evaporated. To the residue was added ice-water, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate, and the solvent was evaporated to give ethyl (methyl) 7-bromo-5-hydroxy-1-tosyl-2,3-dihydro-1H-1-benzazepine-4-**[carb oxylate]** **carboxylate** (mixture) (153 g) as white crystals.

Page 111, paragraph 2 (AMENDED)

Reference Example 22

To anhydrous acetic acid (0.84 ml) was added dropwise formic acid (0.4 ml), under ice-cooling, and the mixture was stirred, under nitrogen atmosphere, at 50 °C for 2 hours. To the mixture was added THF (5 ml), and to the mixture was added dropwise, under ice-cooling, a solution of methyl 7-bromo-2,3-dihydro-1H-1-benzazepine-4- **[carboxy late]** **carboxylate** (1.0 g) in THF (15 ml). The mixture was stirred at room temperature overnight. The solvent was

[redacted]

evaporated, and to the residue was added water. The mixture was extracted with ethyl acetate. The organic layer was washed with sodium hydrogen carbonate solution, water **[an]** **and** saturated brine and dried with anhydrous magnesium sulfate. The solvent was evaporated to give methyl 7-bromo-1-formyl-2,3-dihydro-1H-1-benzazepine-4-carboxylate (1.07 g) as colorless crystals.

Page 133, paragraph 2 (AMENDED)

Reference Example 46

In methanol (25 ml) and THF (25 ml) was dissolved methyl 7-[4-(2-butoxyethoxy)phenyl]-1-formyl-2,3-dihydro-1H-1- **[benzaz epine]** **benzazepine** -4-carboxylate (0.23 g). To the solution was added 1N sodium hydroxide solution (5 ml), and the mixture was stirred at 55 °C for 1.5 hours and concentrated. To the residue was added water, and the mixture was neutralized **[with1IN]** **with 1N** hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate, and the solvent was evaporated to give 7-[4-(2-butoxyethoxy)phenyl)-1-formyl-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (0.24 g) as colorless amorphous.

Page 154, paragraph 2 (AMENDED)

Reference Example 68

In a mixture of THF and ethanol (1:1, v/v, 10.0 ml) was dissolved **[methyl1]** **methyl 1**-acetyl-7-[4-(4-morpholino)phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylate (394 mg). To the solution was added 1N sodium hydroxide solution (3.0 ml), and the mixture was stirred at room temperature for 12 hours. To the mixture was added 1N hydrochloric acid to convert **to a** weakly acidic solution, and the mixture was extracted with ethyl acetate. The organic layer was dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to

give 1-acetyl-7-[4-(4-morpholino)phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (372 mg, 98%) as pale yellow crystals.

Page 157, paragraph 1 (AMENDED)

mixture was heated to reflux under argon atmosphere for 14.5 hours. The mixture was diluted with ethyl acetate, and washed with water and saturated brine, and the organic layer was dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified with silica gel column chromatography (75 g, hexane: ethyl acetate = 3 : 1) to give methyl 1-(t-butoxycarbonyl)-7-(4- **[ropoxyphenyl]** **<u>propoxyphenyl</u>**)-2,3-dihydro-1H-1-benzazepine-4-carboxylate as yellow amorphous. The obtained methyl 1-(t-butoxycarbonyl)-7-(4-propoxyphenyl)-2,3-dihydro-1H-1-benzazepine-4-carboxylate was dissolved in ethyl acetate (80 ml). To the solution was added 6N hydrochloric acid (20 ml) at room temperature, and the mixture was stirred at 100°C for 30 minutes and neutralized with 1N sodium hydroxide and saturated sodium hydrogen carbonate solution. The separated organic layer was washed with saturated sodium hydrogen carbonate solution, water and saturated brine, and dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure to give crystals, which were washed with ethyl acetate/hexane to give methyl 7-(4-propoxyphenyl)-2,3-dihydro-1H-1-benzazepine-4-carboxylate (947 mg) as yellow crystals. The mother liquor was concentrated, and the residue was purified with silica gel column chromatography (15 g, hexane:ethyl

Page 163, paragraph 1 (AMENDED)

the residue was purified with silica gel column chromatography (75 g, hexane: ethyl acetate = 4:1) to give methyl 1-(t-butoxycarbonyl)-7-(4-ethoxy-3-fluorophenyl)-2,3- **[dihydoro]** **dihydro** -1H-1-benzazepine-4-carboxylate as yellow amorphous. The obtained methyl 1-(t-butoxycarbonyl)**-[7-(4-ethoxy-3-fluorophenyl)-2,3-dihydro-1-(t-butoxycarbonyl)-]**7-(4-ethoxy-3-fluorophenyl)-2,3- **[dihydoro]** **dihydro** -1H-1-benzazepine-4-carboxylate was dissolved in ethyl acetate (80 ml). To the solution was added 1N hydrochloric acid (15 ml) at room temperature, and the mixture was stirred at 100 °C for 1 hour and neutralized with 1N sodium hydroxide and saturated sodium hydrogen carbonate solution. To the mixture was added ethyl acetate, and the separated organic layer was washed with saturated sodium hydrogen carbonate solution, water and saturated brine, and dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified with silica gel column chromatography (50 g, hexane: ethyl acetate = 9: 1 → 4:1 → 2: 1) to give methyl 7-(4-ethoxy-3-fluorophenyl)-2,3-dihydro-1H-1-benzazepine-4-carboxylate (1007 mg, 86 %) as yellow crystals.

Page 188, paragraph 1 (AMENDED)

Working Example 1 (Production of Compound 1)

In DMF (10 ml) was dissolved 7-[4-(2-ethoxyethoxy)phenyl]-1-formyl-2,3-dihydro-1H-1-benzazepine 4-carboxylic acid (0.18 g). To the solution was added, under ice-cooling, thionyl chloride (0. 09 ml), and the mixture was stirred at room temperature for 30 minutes. Under reduced pressure, the solvent was evaporated, and the residue was dissolved in THF (20 ml). The solution was added dropwise to a solution of 4-[N-methyl-N-(tetrahydro-2H-pyran-4-

yl)aminomethyl]aniline (0.12 g) and triethylamine (0.33 ml) in THF (10 ml), under ice-cooling, and the mixture was stirred under nitrogen atmosphere at room temperature overnight. Under reduced pressure, the solvent was evaporated. To the residue was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate, and the solvent was evaporated to give crude crystals, which were recrystallized from ethyl acetate/hexane to give 7-[4-(2-ethoxyethoxy)phenyl]-1-formyl-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1H-1-benzazepine-4- **[carboxalnide]** **carboxamide** (Compound 1) (0.23g) as colorless crystals.

Page 191, paragraph 1 (AMENDED)

and the mixture was stirred at room temperature for 30 minutes. Under reduced pressure, the solvent was evaporated, and the residue was dissolved in THF (25 ml). The solution was added dropwise **to** a solution of 4-[N-methyl-N-(**[tetrayhydro]** **tetrahydro** -3H-pyran-4-yl)aminomethyl]aniline (0.15 g), and triethylamine (0.4 ml) in THF (5 ml), under ice-cooling, and the mixture was stirred under nitrogen atmosphere at room temperature overnight. Under reduced pressure, the solvent was evaporated. To the residue was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate, and the solvent was evaporated to give crude crystals, which were recrystallized from ethanol to give 7-[4-(2-butoxyethoxy)phenyl]-1-formyl-N-[[4-[(N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino)methyl]phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxamide (Compound 3) (0.23 g) as colorless crystals.

Page 197, paragraph 2 (AMENDED)

Working Example 8 (Production of Compound 8)

In THF (5 ml) was dissolved 7-[4-(3-ethoxypropoxy)phenyl]-1-methanesulfonyl-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (0.20 g). To the solution were added, under ice-cooling, thionyl chloride (0.06 ml) and DMF (catalytic amount), and the mixture was stirred at room temperature for 2 hours. Under reduced pressure, the solvent was evaporated, and the **[residua]** **residue** was dissolved in THF (15 ml). The solution was added dropwise to a solution of 4-[N-methyl-N-(tetrahydro-2H-pyran-4-yl)aminomethyl]aniline (0.11 g) and triethylamine (0.19 ml) in THF (5 ml), under ice-cooling, and the mixture was

Page 203, paragraph 2 (AMENDED)

Working Example 12 (Production of Compound 12)

In a mixture of water: ethanol: toluene (1: 1: 10, v/v, 18.0 ml) were dissolved 4-(2-propoxyethoxy)phenyl borate (242 mg) and 7-bromo-1-methyl-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1H-1-benzazepine-4- **[carboxarnide]** **carboxamide** (436 mg). To the solution was added potassium carbonate (299 mg), and the mixture was stirred under argon atmosphere at room temperature for 30 minutes. To the mixture was added tetrakistriphenylphosphinepalladium (42 mg), and the mixture was heated to reflux under argon atmosphere for 10 hours. The mixture was diluted with ethyl acetate, and washed with water and saturated brine, and the organic layer was dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified with silica gel column chromatography (30 g, ethyl acetate: ethanol: **[triethylalnine]** **triethylamine** = 180: 20: 1) and recrystallized from ethanol/hexane to give 1-methyl-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-7-[4-(2-propoxyethoxy)phenyl]-2,3-

dihydro-1H-benzazepine-4-carboxamide (Compound 12) (186 mg, 35%) as yellow crystals.

Page 206, paragraph 1 (AMENDED)

room temperature for 30 minutes. Under reduced pressure, the solvent was evaporated, and to the residue was added THF (15.0 ml). On the other hand, to 4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]aniline dihydrochloride (337 mg) was added THF (10.0 ml), and then was added triethylamine (1.00 ml). To the obtained mixture was added dropwise at 0 °C the previously prepared acid chloride suspension, and the mixture was stirred at room temperature for 15 hours. To the mixture was added ethyl acetate, and the mixture was washed with water and saturated brine. The organic layer was dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified with silica gel column chromatography (35 g, ethyl acetate → ethyl acetate: ethanol = 10: 1 → ethyl acetate: ethanol: triethylamine = 100: 10: 1) and recrystallized from ethanol to give 1-formyl-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-7-[4-(2-propoxy)ethoxyphenyl]-2,3-dihydro-1H-1-benzazepine-4- **[carboxarnide]** **carboxamide** (Compound 14) (459 mg, 80 %) as white crystals.

Page 212, paragraph 1 (AMENDED)

dihydro-1H-1-benzazepine-4-carboxamide (440 mg). To the solution was added potassium carbonate (301 mg), and the mixture was stirred under argon atmosphere at room temperature for 30 minutes. To the mixture was added tetrakistriphenylphosphinepalladium (42 mg), and the mixture was refluxed under argon atmosphere for 10 hours. The mixture was diluted with ethyl acetate, and washed with water and saturated brine, and the organic layer was dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified with silica gel column chromatography (30 g, ethyl acetate → ethyl acetate:

ethanol = 10: 1 → ethyl acetate: ethanol: triethylamine = 100: 10: 0.5) and recrystallized from ethyl acetate/IPE to give 7-[4-(2- **[butoxYethoxy]** **butoxyethoxy**)phenyl]-1-methyl-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxamide (Compound 18) (287 mg, 53 %) as yellow crystals.

Page 216, paragraph 2 (AMENDED)

Working Example 21 (Production of Compound 21)

In a mixture of water: ethanol: toluene (1: 1: 10, v/v, 18.0 ml) were dissolved 3-chloro-4-(2-ethoxy)ethoxyphenyl borate (280 mg) and 7-bromo-1-formyl-N-[4-[[N-methyl-N-(tetrahydro-2H-pyran-4-yl)amino]methyl]phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxamide (380 mg). To the solution was added potassium carbonate (253 mg), and the mixture was stirred under argon atmosphere at room temperature for 30 minutes. To the mixture was added **[tetrkistriphenylphosphinepalladium]** **tetrakistriphenylphosphinepalladium** (35 mg) , and the mixture was heated to reflux under argon atmosphere for 10 hours. The mixture was diluted with ethyl acetate, and washed with water and saturated brine, and the organic layer was dried with anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure, and the residue was purified with silica gel column chromatography (25 g, ethyl acetate → ethyl acetate: ethanol = 10: 1 → ethyl acetate: ethanol: **[triethylarnine]** **triethylamine** = 100 : 10: 0.5) and recrystallized from ethanol to give 7-[3-chloro-4-(2-ethoxy)ethoxyphenyl]-1-

Page 228, paragraph 2 (AMENDED)

Working Example 30 (Production of Compound 30)

In DMF (6 ml) was dissolved 1-butyl-7-[4-(**[2-propxyethoxy]** **2-propoxyethoxy**)phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (0.30 g). Under ice-cooling, to the mixture was added thionyl chloride (0.15 ml). The mixture was stirred at

room temperature for 30 minutes. The solvent was evaporated under reduced pressure. In THF (20 ml) was suspended the residue, and the suspension was added dropwise to a solution of 4-[N-methyl-N-

Page 231, paragraph 2 (AMENDED)

Working Example 32 (Production of Compound 32)

In DMF (4 ml) was dissolved 1-benzyl-7-[4-(**[2-propxyethoxy]** **2-propoxyethoxy**)phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (0.15 g). Under ice-cooling, to the mixture was added thionyl chloride (0.06 ml). The mixture was stirred at room temperature for 30 minutes. The solvent was evaporated under reduced pressure. In THF (25 ml) was dissolved the residue, **and then** the solution was added dropwise to a solution of 4-[N-methyl-N-(tetrahydro-2H-pyran-4-yl)aminomethyl]aniline (0.09 g) and triethylamine (0.23 ml) in THF (10 ml), under ice-cooling. The mixture was stirred at room temperature overnight under nitrogen atmosphere. The solvent was evaporated under reduced **[solvent]** **pressure**. Water was added to the mixture, **and then** the mixture was extracted with ethyl acetate. The organic layer was

Page 255, paragraph 2 (AMENDED)

Reference Example 99

In methanol (25 ml) and THF (25 ml) was dissolved methyl 1-propionyl-7-(**[2-propoxyethxy]** **2-propoxyethoxy**)-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.2 g), and to the solution was added 1N sodium hydroxide solution (5 ml). The mixture was stirred at room temperature overnight, concentrated**[.]** **, and then** neutralized with 1N hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with water and saturated brine, and

dried with anhydrous magnesium sulfate. The solvent was evaporated to give 1-propionyl-7-(2-propoxyethoxy)-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (0.2 g) as colorless crystals.

Page 263, paragraph 2 (AMENDED)

Reference Example 109

In **[methnol]** **methanol** (10 ml) and THF (10 ml) was dissolved methyl 1-benzyl-7-[4-(2-propoxyethoxy)phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.27 g). To the solution was added 1N sodium hydroxide solution (10 ml), and the mixture was stirred at room temperature overnight

Page 265, paragraph 2 (AMENDED)

Reference Example 111

In **[methnol]** **methanol** (25 ml) and THF (25 ml) was dissolved methyl 1-benzyl-7-[4-(2-butoxyethoxy)phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.49 g). To the solution was added 1N sodium hydroxide solution (10 ml), and the mixture was heated at 50 °C overnight and concentrated, **[which was]** **then** neutralized with 1N hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate. The solvent was evaporated to give 1-benzyl-7-[4-(2-butoxyethoxy)phenyl]-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (0.47 g) as yellow crystals.

Page 343, paragraph 2 (AMENDED)

Working Example 81 (Production of Compound 81)

A catalytic amount of N,N-dimethyl-4-aminopyridine was added to a solution of 7-butoxyethoxyphenyl)-1-[(4-methylthiazol-5-yl)methyl]-2,3-dihydro-1-benzazepine-4-carboxylic

acid (150 mg), 4-[[N-methyl-N-(tetrahydropyran-4-yl)amino]methyl]aniline (88 mg) and 1-hydroxybenzotriazole (96 mg) in DMF (15 ml), followed by addition of 1-ethyl-3-(3-**[dimethylaminopropylcarbodiimede]** **dimethylaminopropylcarbodiimide** (137 mg). The mixture was stirred under nitrogen atmosphere at room temperature overnight. To the mixture was added water, and the mixture was extracted with ethyl **[acetated]** **acetate**. The organic layer was washed with saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, and the resulting residue was separated and purified with silica gel column chromatography (methanol: ethyl acetate = 1:3) to give 7-(4-butoxyethoxyphenyl)-N-[4-[[N-methyl-N-tetrahydropyran-5-yl)amino]methyl]phenyl]-1-[(4-methylthiazol-5-yl)methyl]-2,3-dihydro-1-benzazepine-4-carboxamide (Compound 81) (7 mg) as yellow amorphous.

Page 351, paragraph 2 (AMENDED)

Reference Example 153

To a solution of methyl 7-(**[propxyethoxyphenyl]** **propoxyethoxyphenyl**)-2,3-dihydro-1-benzazepine-4-carboxylate (300 mg) and 2-methoxybenzaldehyde (535 mg) in 1,2-dichloroethane (10 ml) was added sodium triacetoxyborohydride (749 mg), and the mixture was stirred under nitrogen atmosphere at room temperature overnight. Then, water was added thereto and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure and the resulting residue was purified with silica gel column chromatography (hexane: ethyl acetate = 3:1) to give methyl (1-(2-methoxybenzyl)-7-(4-propoxyethoxyphenyl)-2,3-dihydro-1-benzazepine-4-carboxylate (394 mg) as yellow oil.

Page 355, paragraph 2 (AMENDED)

Reference Example 157

To a suspension of 60% sodium hydride (0.23 g) in tetrahydrofuran (5 ml) which had been washed with hexane three times was added dropwise a solution of methyl 7- **[buromo]** **bromo** -2,3-dihydro-1-benzazepine-4-carboxylate (0.80 g) in tetrahydrofuran (10 ml) under nitrogen atmosphere at 0 °C. The temperature was returned to room temperature and the mixture was stirred for 1 hour. Then, to the mixture was added dropwise a solution of 3-methoxybenzyl bromide (2.29 g) in tetrahydrofuran (5 ml) at 0 °C. The temperature was returned to room temperature, and the mixture was stirred for 3 days. To the mixture were added ethyl acetate and water, and the mixture was separated. The organic layer was washed with saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure and the resulting residue was purified with silica gel column chromatography (hexane: ethyl acetate = 5: 1) to give methyl 7-bromo-1-(3-methoxybenzyl)-2,3-dihydro-1-benzazepine-4-carboxylate (0.69 g) as yellow oil.

Page 393, paragraph 1 (AMENDED)

water at 0 °C, and 1N hydrochloric acid was further added to **[neutral]** **neutralize**, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, which was recrystallized from hexane-ethyl acetate to give 7-(4-butoxyethoxyphenyl)-1-[(1- **[mehylpyrazol]** **methylpyrazol** -4-yl)methyl]-2,3-dihydro-1-benzazepine-4-carboxylic acid (239 mg) as yellow crystals.

Page 412, paragraph 2 (AMENDED)

Reference Example 223

To a solution of methyl 7-bromo-2,3-dihydro-1-benzazepine-4- **[carobxylate]** **carboxylate** (200 mg) and pyridine (123 mg) in tetrahydrofuran (10 ml) was added 2- **[thenoyl]** **thienyl** chloride (208 **[gmg]** **mg**) at 0 °C, and the mixture was heated at 78 °C overnight. After allowing to cool, to the mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with magnesium sulfate. The solvent was evaporated, which was recrystallized from hexane-ethyl acetate to give methyl 7-bromo-1-(2-thienylcarbonyl)-2,3-dihydro-1-benzazepine-4-carboxylate (236 mg) as colorless crystals.

Page 424, paragraph 2 (AMENDED)

Reference Example 236

In toluene (100 ml), ethanol (10 ml) and water (10 ml) were suspended methyl 7-bromo-2,3-dihydro-1-benzazepine-4- **[caroxyalte]** **carboxylate** (3.0 g), 4-propoxyethoxyphenyl borate (3.1 g) and potassium carbonate (3.8 g), and the suspension was stirred for 30 minutes under argon atmosphere. Then, to the suspension was added **[tetrakistriphenylphosphinepalldium]** **tetrakistriphenylphosphinepalladium** (860 mg), and the mixture was heated at 100 °C for 8 hours under argon atmosphere. After allowing to cool, water was added thereto, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, and the resulting residue was purified with silica gel column chromatography (hexane: ethyl acetate = 3: 1) to give the solid, which was washed with hexane to give methyl 7-(4-propoxyethoxyphenyl)-2,3-dihydro-1-benzazepine-4-carboxylate (2.59 g) as yellow crystals.

Page 425, paragraph 2 (AMENDED)

Reference Example 237

In toluene (200 ml) and ethanol (35 ml) were suspended methyl 7-bromo-2,3-dihydro-1-benzazepine-4-carboxylate (5.0 g), 4- **[butoethoxyphenyl]** **butoxyethoxyphenyl** borate (4.6 g) and 1M potassium carbonate solution (35 ml), and the mixture was stirred for 30 minutes under argon atmosphere. Then, to the mixture was added tetrakistriphenylphosphinepalladium (1 g), and the mixture was heated at 100 °C overnight under argon atmosphere. After allowing to cool, to the mixture was added water, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, and the resulting residue was purified with silica gel column chromatography (hexane: ethyl acetate = 4:1) to give the solid, which was washed with hexane to give methyl 7- (4-butoxyethoxyphenyl)-2,3-dihydro-1-benzazepine-4- **[carboxyalte]** **carboxylate** (5.7 g) as yellow crystals.

Page 430, paragraph 2 (AMENDED)

Reference Example 243

In toluene (15 ml), ethanol (1.5 ml) and water (1.5 ml) were suspended methyl 7-bromo-[(1-ethylpyrazol-4-yl)methyl]-2,3-dihydro-1-benzazepine-4- **[caroxyalte]** **carboxylate** (550 mg), 4-propoxyethoxyphenyl borate (320 mg) and potassium carbonate (506 mg), and the suspension was stirred for 30 minutes under argon atmosphere. Then, to the suspension was added tetrakistriphenylphosphinepalladium (81 mg), and the mixture was heated at 100 °C for 6 hours under argon atmosphere. After allowing to cool, water was added thereto, and the mixture was extracted with ethyl acetate. The organic layer was washed with saturated brine and dried with magnesium sulfate. The solvent was evaporated under reduced pressure, and the resulting residue was purified with silica gel column chromatography (hexane: ethyl acetate = 1:1) to give

methyl 1-[(1-ethylpyrazol-4-yl)methyl]-7-(4-propoxyphenyl)-2,3-dihydro-1-benzazepine-4-carboxylate (370 mg) as yellow oil.

Page 432, paragraph 1 (AMENDED)

In methanol (25 ml) and THF (10 ml) was dissolved methyl 7-[(4-(2-butoxyethoxy)phenyl]-1-(2- **[methyothiazol]** **methylthiazol** -4-yl)-2,3-dihydro-1H-1-benzazepine-4-carboxylate (0.17 g). To the solution was added 1N sodium hydroxide solution (4 ml), and the mixture was stirred at room temperature overnight, heated at 60 °C for 5 hours, concentrated, neutralized with 1N hydrochloric acid and extracted with ethyl acetate. The organic layer was washed with water and saturated brine and dried with anhydrous magnesium sulfate. The solvent was evaporated to give 7-[4-(2-butoxyethoxy)phenyl]-1-(2-methylthiazol-4-yl)-2,3-dihydro-1H-1-benzazepine-4-carboxylic acid (0.12 g) as yellow crystals.

Page 436, paragraph 2 (AMENDED)

Reference Example 249

In toluene/ethanol/water (=10/1/1, 41 ml) was dissolved methyl 7-bromo-1-isobutyl-2,3-dihydro-1-benzazepine-4- **[caroxylate]** **carboxylate** (0.90 g). To the solution were added 4-(2-propoxyethoxy)phenyl borate (0.72 g) and potassium carbonate (0.81 g) and the mixture was stirred for 30 minutes under argon atmosphere. To the mixture was added tetrakistriphenylphosphinepalladium (123 mg) and the mixture was heated to reflux for 14 hours. After **[cooled]** **cooling** to room temperature, the solution was added to water, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, and dried with magnesium sulfate. The solvent was removed under

Page 494, paragraph 1 (AMENDED)

room temperature, and the solvent was removed under reduced pressure. The resulting residue was added to water, and the mixture was extracted with ethyl acetate. The extract was washed with saturated brine, and dried with magnesium sulfate. The solvent was removed under reduced pressure, and the resulting residue was purified with silica gel column chromatography (ethyl acetate/ethanol = 15: 1) to give methyl 7-[4-(2-butoxyethoxy)phenyl]1-(tetrazol-5- **[ylemethyl] ylmethyl**)-2,3-dihydro-1-benzazepine-4-carboxylate (0.67 g).

Page 523, paragraph 2 (AMENDED)

Reference Example 306

To a solution of methyl 7-[4-(2-butoxyethoxy)phenyl-1-[(2-methyl-1,3-dioxolan-2-yl)methyl]-7-[4-(2-propoxyethoxy)phenyl]-2,3-dihydro-1H-1- **[benzaepine] benzazepine** -4-carboxylate (795.7 mg) in a mixture of THF-methanol (5-5 ml) was added 1N sodium hydroxide solution

Page 529, paragraph 2 (AMENDED)

Reference Example 311

4-morpholinophenyl borate (237 mg) and 7-bromo-1-propyl-N-[4-[[N-methyl-N-(**[terahydropyran] tetrahydropyran** -4-